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Prevalence and Clinical Manifestations of 22q11.2 Microdeletion in Adults With Selected Conotruncal Anomalies

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OBJECTIVES This study was designed to determine the prevalence and clinical manifestations of 22q11.2 microdeletion in adults with selected conotruncal anomalies and to assess the clinician's ability to predict the presence or absence of 22q11.2 microdeletion on the basis of clinical features.

BACKGROUND It is known that 22q11.2 microdeletion is a chromosomal anomaly with cardiac and extracardiac manifestations. The prevalence and manifestations in adults have not been well characterized.

METHODS A total of 103 consecutive adults with either tetralogy of Fallot (TOF), pulmonary atresia/ventricular septal defect (PA/VSD), or truncus arteriosus (TA) were prospectively screened for 22q11.2 microdeletion using a fluorescence in situ hybridization (FISH) assay. Clinicians were asked to predict 22q11.2 microdeletion status on the basis of clinical features. A geneticist blinded to FISH assay results reviewed photographs of the patients for typical dysmorphic features of 22q11.2 microdeletion.

RESULTS Six patients (prevalence 5.8%, 95% confidence interval 1.3 to 10.3) had 22q11.2 microdeletion (3 with TOF, 2 with PA/VSD, 1 with TA). In two of these patients, the clinician incorrectly predicted absence of the deletion. In three, typical dysmorphic features of 22q11.2 microdeletion were absent.

CONCLUSIONS Our work showed that 22q11.2 microdeletion is under-recognized in adults with congenital heart disease. The absence of typical phenotypic features makes it difficult to correctly predict if the deletion is present. Screening for 22q11.2 microdeletion should be considered in adults with high-risk cardiac lesions, as it has important implications in reproductive counseling and surveillance for associated extracardiac manifestations. (J Am Coll Cardiol 2005;45:595–8)
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The 22q11.2 microdeletion syndrome is characterized by a hemizygous deletion that encompasses several genes on chromosome 22q11.2. Mutation of the TBX1 gene has recently been suggested as a major determinant of the syndrome (1). The deletion usually arises spontaneously and is relatively common (1 in 4,000 to 6,000 live births) (2). The 22q11.2 microdeletion is found in the majority of patients with DiGeorge syndrome and velocardiofacial and conotruncal anomaly face syndromes, suggesting that these syndromes represent a spectrum of phenotypic expression of the deletion (3). Typically, the associated cardiac anomalies involve the conotruncus and include lesions such as tetralogy of Fallot (TOF), pulmonary atresia/ventricular septal defect (PA/VSD), and truncus arteriosus (TA) (3). The purpose of this study was to determine the prevalence and clinical manifestations of 22q11.2 microdeletion in adults with selected conotruncal anomalies and to assess the ability of clinicians to predict the presence of 22q11.2 microdeletion.

METHODS

From October 2001 to September 2003, all patients with TOF, PA/VSD, or TA who had prescheduled appointments in the adult congenital heart disease clinic at the Mayo Clinic were identified. At the time of routine diagnostic venipuncture, an extra 5 ml of blood was drawn and sent for cytogenetic analysis only after consent from the patient was obtained. The study was approved by the Mayo Clinic Institutional Review Board.

FISH. Fluorescence in situ hybridization (FISH) was performed with a critical region probe for the DiGeorge/velocardiofacial syndrome chromosome region (Vysis probe set for TUPLE-1) of chromosome 22 (22q11.2) (4).

Clinical evaluation. During the clinic visit a questionnaire was conducted. Photographs of frontal and lateral facial views and both hands were taken. The clinician was asked to predict 22q11.2 microdeletion status on the basis of the available clinical information and physical features; the clinician was blinded to the results of the FISH analysis. A

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Abbreviations and Acronyms

CI = confidence interval
FISH = fluorescence in situ hybridization
PA/VSD = pulmonary atresia/ventricular septal defect
TA = truncus arteriosus
TOF = tetralogy of Fallot

geneticist blinded both to the FISH results and clinical features independently reviewed the patient's photographs to determine the presence of the typical dysmorphic features of 22q11.2 microdeletion. Patients were offered the opportunity to learn their test results, at which time counseling by a physician was provided. Patients with the deletion were referred to medical genetics for further assessment and counseling.

RESULTS

Cohort. A total of 104 consecutive patients were offered screening. One patient declined; this patient did not have features to suggest 22q11.2 microdeletion. Thereafter, 103 patients underwent testing with FISH analysis (mean age 40 ± 12 years, range 18 to 70 years). The intracardiac diagnoses consisted of TOF in 77 patients, PA/VSD in 23, and TA in 3.

Patients with 22q11.2 deletion. Six patients (5.8%, 95% confidence interval [CI] 1.3 to 10.3) were found to have a 22q11.2 microdeletion (Tables 1 and 2). The prevalence for each diagnosis was TOF 3.8% (95% CI 0 to 8.2), PA/VSD 8.7% (95% CI 0 to 20.2), TA 33.3% (95% CI 0 to 86.7). Two patients had children. Patient #1 had a healthy female child without 22q11.2 microdeletion. Patient #3 had a female child with 22q11.2 microdeletion and truncus arteriosus.

Clinical prediction and presence of dysmorphic features. In two of the patients with 22q11.2 microdeletion, the clinician incorrectly predicted absence of the microdeletion. The 22q11.2 microdeletion was predicted in nine patients who were found to be negative on FISH analysis (Table 3). Of the 103 patients, 93 agreed to have their photographs taken. Three of the six FISH-positive patients were found by the geneticist to have typical dysmorphic features of 22q11.2 microdeletion on the basis of the photographs; five FISH-negative patients had typical or suggestive dysmorphism of 22q11.2 on the basis of the photographs.

DISCUSSION

The prevalence of 22q11.2 microdeletion found in our study for each cardiac anomaly was lower than what has been reported in published pediatric reports (TOF 6% to 21%, PA/VSD 32% to 48%) (5–8). This discrepancy between children and adults may possibly be explained by a higher attrition rate in children with 22q11.2 microdeletion. Indeed, reports have indicated that for PA/VSD, 22q11.2 microdeletion patients have a tendency to have more complex pulmonary artery anatomy when compared with the 22q11.2 microdeletion-negative patients (6,7,9). This may unfavorably affect surgical and percutaneous interventions and long-term outcome. Furthermore, extracardiac complications associated with 22q11.2 microdeletion may affect survival into adulthood (10).

There are few reports that have characterized the adult phenotype of 22q11.2 microdeletion (11–13). There is a suggestion that adults with 22q11.2 microdeletion may have higher rates of learning disabilities, psychiatric disorders, and palate anomalies, but lower rates of congenital heart disease when compared to children (12). However, the majority of adults reported previously were ascertained following diagnosis of affected offspring, which may have introduced bias (12).

The ability of the clinician to predict 22q11.2 microdeletion based on the presence of typical clinical features was difficult. The clinicians both erred in missing and overdiagnosing 22q11.2 microdeletion. These clinicians were experts in adult congenital heart disease, but specific training for the study was not given. Although reports have shown that most 22q11.2 microdeletion patients have at least one extracardiac manifestation that is typical of the microdeletion (14), two of our patients had none. Even though it is possible, therefore, that more extensive education regarding the typical features of 22q11.2 microdeletion may have increased the accuracy of the physicians' predictions, the challenges of accurate clinical diagnosis are evident.

The poor correlation between the presence of typical dysmorphic features and 22q11.2 microdeletion can be explained by several possible factors. The assessment of

Table 1. Cardiac Manifestations of Patients With 22q11.2 Microdeletion (n = 6)

Patient	Age, Gender	Anatomy	Pulmonary Artery	MAPCAs	Arch Side	Arch Vessels
1	26, F	TOF	H and C	N	Right	Normal
2	25, F	TOF	Normal	N	Right	Normal
3	47, M	TOF	Normal	N	Left	Normal
4	26, F	PA/VSD	H and C	Y	Left	Normal
5	32, F	PA/VSD	H and NC	Y	Left	RLSA and RAIV
6	27, F	TA	Normal	N	Left	Normal

C = confluent; H = hypoplastic; MAPCAs = major aortopulmonary collateral arteries; NC = nonconfluent; PA/VSD = pulmonary atresia/ventricular septal defect; RAIV = retro-aortic innominate vein; RLSA = retro-esophageal left subclavian artery; TA = truncus arteriosus; TOF = tetralogy of Fallot.

Table 2. Extracardiac Manifestations of Patients With 22q11.2 Microdeletion (n = 6)

Patient	Palatal Anomalies	Speech Difficulty	Calcium Level	Learning Disability	Psychiatric History	Other
1	Cleft	Y	Normal	N	N	N
2	N	N	Normal	Y	Y	N
3	N	N	Normal	N	N	Thrombocytopenia
4	N	N	Normal	N	N	N
5	N	N	Normal	N	N	N
6	N	N	Normal	Y	N	Hypocalcemia

typical dysmorphic features by the geneticist was based solely on review of the photographs. Also, aging changes or obscuring of features may have been a factor. As for patients who were felt to have typical features but not found to have a 22q11.2 microdeletion, this highlights the difficulties for even the most experienced physician in recognizing the syndrome.

Clinical relevance. Although the 22q11.2 microdeletion is now well described in the pediatric literature, our data suggest there are likely many adults with unrecognized 22q11.2 microdeletion who are followed in adult congenital heart disease clinics. This may be partly explained by the only recent availability of the FISH probe, so that the majority of adults who are presently followed in adult congenital heart disease clinics did not have access to testing at the time when they were under the care of pediatricians (15). Lack of awareness of the clinical features and availability of testing for 22q11.2 microdeletion syndrome may also contribute. Furthermore, our results indicate that 22q11.2 microdeletion may be difficult to detect in the adult population, even by cardiologists with expertise in congenital heart disease.

It is reasonable to postulate that the identification of 22q11.2 microdeletion in the pediatric and adult population most likely optimizes the recognition and management of its extracardiac complications (12). Furthermore, an important issue unique to the adult population is counseling regarding reproduction. Children born to a parent with 22q11.2 microdeletion have a 50% chance of having the deletion themselves, as well as its associated complications (16). This has become even more relevant now that prenatal testing for 22q11.2 microdeletion has become available (16).

Typical features that should alert the clinician of possible presence of 22q11.2 microdeletion in a patient with adult congenital heart disease. The cardiovascular abnormalities that have the highest reported prevalence of 22q11.2 are listed in Table 4. Within the same cardiac diagnoses, patients with 22q11.2 microdeletion are reported to have a higher incidence of right aortic arch, abnormal anatomy of the great arteries, or abnormalities of the pulmonary arteries (3,17). Apart from the cardiac anomalies listed in Table 1, typical extracardiac anomalies that may alert the clinician to underlying 22q11.2 microdeletion are listed in Table 4. Although there is a large phenotypic variability, typical facial features include a long narrow face with flat malar bones, small chin, hooded eyelids, narrow palpebral fissures, "rectangular" nose that can be long with paranasal bossing and a squared or sometimes bulbous tip, small mouth, and small ears with overfolding of the superior helix (Fig. 1) (13). These facial features may be subtle in adults and some can be associated with aging changes in normal individuals (13).

Which adults should be screened? This is a difficult and controversial issue (3,18,19). We suggest that cardiologists should first consider the possibility of underlying 22q11.2 microdeletion when assessing all patients with adult congenital heart disease, especially those with conotruncal anomalies. Presence of high-risk cardiac lesions, or typical associated cardiac and extracardiac anomalies, should prompt consideration of screening and discussion with the patient. The patient should be presented with the pros (screening for extracardiac manifestation, knowledge as to the potential for transmission to offspring) and cons (insurance accessibility) of screening and offered appropriate genetic counseling. If found to be positive, the patient

Table 3. Ability of Clinician to Predict Presence of 22q11.2 Microdeletion Based on the Available Clinical Information and Physical Features (n = 103)

	Clinically Predicted to Be Positive	Clinically Predicted to Be Negative
FISH positive	4	2
FISH negative	9	88

FISH = fluorescence in situ hybridization.

Table 4. Typical Clinical Features That Should Alert the Clinician of Possible Presence of 22q11.2 Deletion

Commonly associated cardiovascular lesions
TOF
PA/VSD
TA
IAA (type B)
Isolated arch anomalies
Extracardiac manifestations
Psychiatric history
Mental retardation
Nonverbal learning disability
Dysmorphic facial features
History of cleft palate
Hypernasal speech
Hypocalcemia

IAA = interrupted aortic arch; PA/VSD = pulmonary atresia/ventricular septal defect; TA = truncus arteriosus; TOF = tetralogy of Fallot.

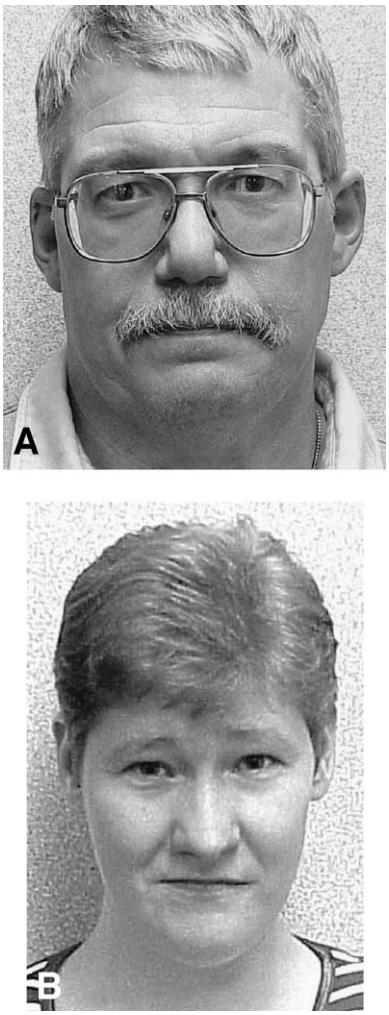

Figure 1. Facial views of two of the patients with 22q11.2 microdeletion illustrating the spectrum of facial dysmorphism. **(A)** Patient #3 in text. Except for mild upper eyelid changes associated with normal aging, this 47-year-old man does not have typical dysmorphic changes of 22q11.2 microdeletion. **(B)** Patient #6 in text. This 27-year-old woman has facial features of 22q11.2 microdeletion including a long face, paranasal bossing, and hooded appearance of the upper eyelids with narrow palpebral fissures.

should undergo investigations to screen for associated anomalies.

Study limitations. The relatively small number of patients with 22q11.2 microdeletion found in our study has prevented us from making meaningful statements on: 1) the phenotype of the adult with 22q11.2 microdeletion; 2) the presence of typical associations with each anatomical defect; and 3) differences between 22q11.2 microdeletion-positive and -negative patients who have conotruncal anomalies.

Conclusions. The 22q11.2 microdeletion syndrome is under-recognized in patients with adult congenital heart disease. It is difficult to determine if the deletion is present or absent solely on the basis of an assessment on phenotypic features. Screening for 22q11.2 microdeletion by FISH analysis should be considered in adult patients with high-risk cardiac lesions, as there are important counseling implications for reproduction and surveillance for associated extracardiac manifestations.

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